# Functional changes of mentalizing network in SCA2 patients: novel insights into understanding the social cerebellum

Article (Unspecified)

# Title Page

## Functional changes of mentalizing network in SCA2 patients: Novel insights into understanding the social cerebellum

Olivito G [1,2,], Siciliano L[3], Clausi S [4] , Lupo M[4], Romano S[5], Masciullo M[6], Molinari M[7], Cercignani M[8], Bozzali M [8,9], Leggio M. [1,4]

1)Department of Psychology, Sapienza University of Rome, Italy

2) IRCCS Santa Lucia Foundation, Rome, Italy

3) PhD Program in Behavioral Neuroscience, Sapienza University of Rome, Italy

4)Ataxia Laboratory, IRCCS Santa Lucia Foundation, Rome, Italy

5)Department of Neurosciences, Mental Health and Sensory Organs (NESMOS), "Sapienza" University of Rome-Sant'Andrea Hospital, Rome, Italy

6) SPInal REhabilitation Lab, IRCCS Fondazione Santa Lucia,Rome, Italy

7)Robotic Neurorehabilitation Lab, Neurorehabilitation 1 and Spinal Center, IRCCS Fondazione Santa Lucia, Rome, Italy.

8)Clinical imaging Science Center, Brighton and Sussex Medical School, Brighton, UK

9)Neuroimaging Laboratory, IRCCS Santa Lucia Foundation, Rome, Italy

Corresponding author:

Dr. Giusy Olivito, PhD
Department of Psychology, Sapienza University of Rome
Via De Marsi,78, 00185, Rome, Italy.
Telephone number: #39-06-51501547
Fax number: #39-06-51501213
E-mail address: g.olivito@hsantalucia.

**Abstract (250)**

In recent years, increasing evidence of the cerebellar role in social cognition has emerged. The cerebellum has been shown to modulate cortical activity of social brain regions serving as a regulator of function-specific mentalizing and mirroring processes. In particular, a mentalizing area in the posterior cerebellum, specifically Crus II, is preferentially recruited for more complex and abstract forms of social processing, together with mentalizing cerebral areas including the dorsal medial prefrontal cortex (dmPFC), the temporo-parietal junction (TPJ) and the precuneus. In the present study, the network-based statistics approach was used to assess functional connectivity (FC) differences within this mentalizing cerebello-cerebral network associated with a specific cerebellar damage. To this aim, patients affected by spinocerebellar ataxia type 2 (SCA2), a neurodegenerative disease specifically affecting regions of the cerebellar cortex, and age-matched healthy subjects have been enrolled. The dmPFC, left and right TPJ, the precuneus and the cerebellar Crus II were used as regions of interest to construct the mentalizing network to be analysed and evaluate pairwise functional relations between them. When compared to controls, SCA2 patients showed altered internodal connectivity between dmPFC, left (L-) and right (R-) TPJ and right posterior cerebellar Crus II.

The present results indicate that FC changes affect a function-specific mentalizing network in patients affected by cerebellar damage. In particular, they allow to better clarify functional alteration mechanisms driven by the cerebellar damage associated to SCA2 suggesting that selective cortico-cerebellar functional disconnections may underlie patients' social impairment in domain-specific complex and abstract forms of social functioning.

**Keywords:**

Cerebellum, cerebral cortex, resting-state fMRI, social cognition, nodes

## 1. Introduction

In recent years, an increasing body of studies focused on the cerebellar role in cognitive functions and emotional regulation also including social cognition abilities [1-10]. From an anatomical point of view, research documented the existence of reciprocal connections between specific cerebellar regions and associative and paralimbic cerebral structures related to emotional and social processing such as the temporo-parietal junction (TPJ), the lateral temporal cortex, the posterior cingulate cortex, the inferior frontal gyrus [11], the amygdala [12] and the insula [13]. Additional insight was derived from the investigation of functional connectivity (FC), that refers to synchronous activation of spatially remote brain regions mediating complex functions and can be measured by using resting-state functional magnetic resonance imaging (RS-fMRI) [14].

Indeed, RS-fMRI studies have demonstrated FC between distinct cerebellar zones and default mode regions in the cerebrum, known to be strictly related to social mentalizing [15-18].

Further evidence has been provided by RS-fMRI studies in subjects with autism spectrum disorders (ASD) [19-22], who typically experience social dysfunctions, showing altered FC within cerebello-cerebral mentalizing networks. Through these circuits, cerebellar dysfunction may affect key social brain regions and impact the social functioning. More recently, altered social performances in patients affected by cerebellar neurodegenerative pathologies with different etiology [2] have been related to cerebello-cerebral FC changes. By using a seed-based approach, these authors found that specific cerebellar subregions of reduced grey matter (GM) in patients also showed altered FC with mentalizing cerebral regions.

Altogether, these findings suggest that there may be a functional topography in the cerebellum for social processing and that some areas of the cerebellum may be preferentially recruited for specific components of the social mentalizing. Indeed, according to the evidence of a topographical organization between function-specific cerebellar networks and function-specific cerebral networks [16; 23], it has been suggested that the cerebellum has a more domain-specific mentalizing

functionality than a domain-general regulatory role [24] since the most cerebellar social-cognitive activity is located within the boundaries of a mentalizing network of the cerebellum [16; 23]. In particular, the cerebello-cerebral network related to the most abstract and complex forms of mentalizing has been characterized by a recent multi-study analysis of Van Overwalle and Marien (2016) [25], and included dorsal medial prefrontal cortex (dmPFC), precuneus/posterior cingulate cortex, bilateral temporo-parietal junction (TPJ) and a region in the posterior cerebellum corresponding to the right Crus II.

Specifically, to test how neural information propagates under social thinking, the authors performed a psycho-physiological interaction (PPI) analysis that covered 5 studies on healthy individuals involving abstract and complex forms of social mentalizing [25] and indicated connectivity from the dmPFC and the right (R-) TPJ to the right posterior cerebellum and back to the left (L-) TPJ [25]. Interestingly, a more recent task-related fMRI study [26] using Dynamic Causal Modeling (DCM) [27] on the same dataset has shown the existence of closed-loop cerebello-cerebral circuits in which effective connections between mentalizing cerebellar and cerebral regions are bidirectional.

In light of all these observations, it is conceivable that FC alterations within this function-specific mentalizing network may be selectively associated with cerebellar damage and account for specific social dysfunctions that have been described in cerebellar patients (for a review see Giocondo and Curcio, 2018) [28]. In this context, while previous findings provided general evidence that cerebellar alterations result in functional connectivity changes related to social impairment [2], investigation of a more homogeneous patients' population, provides additional insight into understanding specific functional alteration mechanisms driven by the cerebellar damage. To test this hypothesis, we used the network-based statistics approach [29] to assess FC at rest within the function-specific mentalizing network that has emerged from the PPI analysis by Van Overwalle and Marien( 2016) [25] in a selected subtype of cerebellar pathology, such as SCA2, a rare

autosomal dominant neurodegenerative disease specifically affecting the cerebellum and characterized by extensive grey matter loss in the cerebellar cortex [30-32].

## 2. Materials and Methods

### *2.1 Subjects*

Ten patients with a genetically confirmed diagnosis of SCA2 [F/M=6/4; mean age ± SD = 47.2± 9.7 years] were recruited from the Ataxia Lab of Fondazione Santa Lucia Hospital. Both in-patients (admitted for rehabilitation) and out-patients (followed up at the clinic) were included. At the time of assessment, all patients had more than 6 months of illness. According to the inclusion criteria, the absence of extra-cerebellar lesion was assessed by an expert neuro-radiologist by visual inspection of the T2-weighted MRI scans acquired as part of this research study. At the time of enrolment, patients did not present with current or past diagnosis of psychiatric disorders.

As showed by the neurological examination, all patients presented with a pure cerebellar syndrome, and no other additional neurological signs except CA-3 that presented a Babinski sign. Cerebellar motor deficits were assessed using the International Cooperative Ataxia Rating Scale [33], whose global score ranges from 0 (absence of any motor deficit) to 100 (presence of motor deficits at the highest degree). As assessed by the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [34-35] patients did not present with general mental processes decline. Some of these patients had participated in previous studies [4; 36; 37].

Demographic and clinical characteristics of the patients are reported in Table 1.

**Table 1.** Demographic characteristics and motor deficit scores of the patients.

| Case code | Age | Gender | IQ | Disease duration (years) | ICARS TOTAL SCORES | CGA Repeats |
|---|---|---|---|---|---|---|
| CA-1 | 42 | F | 74 | 1 | 47 | 22/39 |
| CA-2 | 42 | F | 81 | 1 | 28 | 14/47 |
| CA-3 | 54 | F | 85 | 1 | 27 | 22/37 |
| CA-4 | 36 | F | 91 | 8 | 37 | 22/42 |
| CA-5 | 65 | M | 82 | 3 | 27 | 22/35 |
| CA-6 | 44 | F | 98 | 13 | 28 | * |
| CA-7 | 62 | F | 75 | 4 | 31 | 22/37 |
| CA-8 | 41 | M | 91 | 3 | 18 | 22/38 |
| CA-9 | 42 | M | 81 | 1 | 24 | 22/39 |
| CA-10 | 44 | M | 110 | 7 | 17 | 22/39 |

**Table 1.** The table reports for each patient age, gender, disease duration (in years) , intellectual level as assessed by the Wechsler Adult Intelligence Scale-Revised (IQ: Intelligence Quotient), total motor scores as assessed by the International Cooperative Ataxia and CAG repeats. *Genetic data are not available for the patient CA-6 because, at the time of the diagnosis, the genetic testing did not include the triplets number counting.

A group of 23 healthy subjects (HS) [F/M=17/6] ranging from 40 to 60 years of age [mean age ± SD = 52.1 ± 5.2 years] with no history of neurological or psychiatric illness were also recruited as control group. T-test and *chi square* analysis ensured that there was no significant difference between the two groups in the mean age (T-value=-1.9; $p$=0.06) and gender distribution ( $X^2$=0.63; $p$=0.42).

This research study was approved by the Ethics Committee of Fondazione Santa Lucia, according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from every participant.

*2.2 MRI acquisition protocol*

All participants underwent an MRI examination at 3T (Philips Achieva using a 32-channels head coil) that included the following acquisitions: 1) dual-echo turbo spin echo [TSE] (TR = 6190 ms, TE = 12/109 ms); 2) fast-FLAIR (TR = 8170 ms, 204TE = 96 ms, TI = 2100 ms); 3) 3D Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR = 1338 ms, TE = 2.4 ms, Matrix = 256 × 224 × 176, in-plane FOV = 250 × 250 mm2, slice thickness = 1 mm); 3) T2* weighted echo planar imaging (EPI) sensitized to blood oxygenation level dependent imaging (BOLD) contrast (TR: 2080 ms, TE: 30 ms, 32 axial slices parallel to AC-PC line, matrix: 64×64, pixel size: 3×3 mm2, slice thickness: 2.5 mm, flip angle: 70°) for resting state fMRI. BOLD echo planar images were collected during rest for a 7 min and 20 s period, resulting in a total of 220 volumes. During this acquisition, subjects were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep. The total scan time was approximately 50 minutes. The TSE scans of patients, acquired as part of this research study, were reviewed by an expert neuroradiologist in order to characterize the brain anatomy and ensure the absence of macroscopic structural abnormalities involving extracerebellar structures. For the control group, conventional MRI scans were inspected in order to exclude any pathological conditions according to the inclusion criteria.

*2.3 Resting state fMRI data pre-processing*

Data were pre-processed using Statistical Parametric Mapping [Wellcome Department of Imaging Neuroscience; SPM8 (http://www.fil.ion.ucl.ac.uk/spm/)], and in-house software implemented in Matlab (The Mathworks Inc, Natick, Massachussetts, USA). For each subject, the first four

volumes of the fMRI series were discarded to allow for T1 equilibration effects. The pre-processing steps included correction for head motion, compensation for slice-dependent time shifts, normalization to the EPI template in MNI coordinates provided with SPM8, and smoothing with a 3D Gaussian Kernel with 8mm$^3$ full-width at half maximum. For each data set the motion parameters estimated during correction were checked to ensure that the maximum absolute shift did not exceed 2 mm and the maximum absolute rotation did not exceed 1.5°. The global temporal drift was removed using a 3$^{rd}$ order polynomial fit and the signal was regressed against the realignment parameters, and the signal averaged over whole brain voxels, to remove other potential sources of bias. Then, all images were filtered by a phase-insensitive band-pass filter (pass band 0.01-0.08 Hz) to reduce the effect of low frequency drift and high frequency physiological noise. Every participant's MDEFT was segmented in SPM in order to estimate the total GM volume and exclude FC differences between the two groups due to macroscopic atrophy patterns. Differences in total GM volumes between patients and controls were excluded (T-value=-0.2; p=0.81).

### *2.4 Statistical Analysis*

#### *2.4.1 Network Based Statistics*

The "Networks-based statistics" (NBS) tool developed by Zalesky and co-authors (2010) [29] was used. According to Van Overwalle and Marien (2016) [25], we used the 5 regions that were associated to abstract mentalizing to construct the *graph.* The graph model of the brain is an abstract structure used to represent pairwise relations between interregional ensembles of neuronal elements, referred to as nodes [29]. Regions on interests (ROIs), referred to as nodes of the mentalizing network, were built using MarsBaR (MARSeille Boîte À Région d'Intérêt), a region of interest (ROI) tool interfacing with SPM [38] and then resliced into EPI standard space. ROIs in the cerebrum were created by taking a sphere with a radius of 8mm around the center and included the dorsal mPFC (centered at 0 50 35), bilateral TPJ (centered at ±50 −55 25) and precuneus/posterior cingulate (centered at 0 −60 40). ROI in the cerebellum was created with a

5mm radius sphere centered at 25 −75 −40 and corresponding to right Crus II (see Figure. 1) (see Van Overwalle and Marien, 2016 for a review) [25].

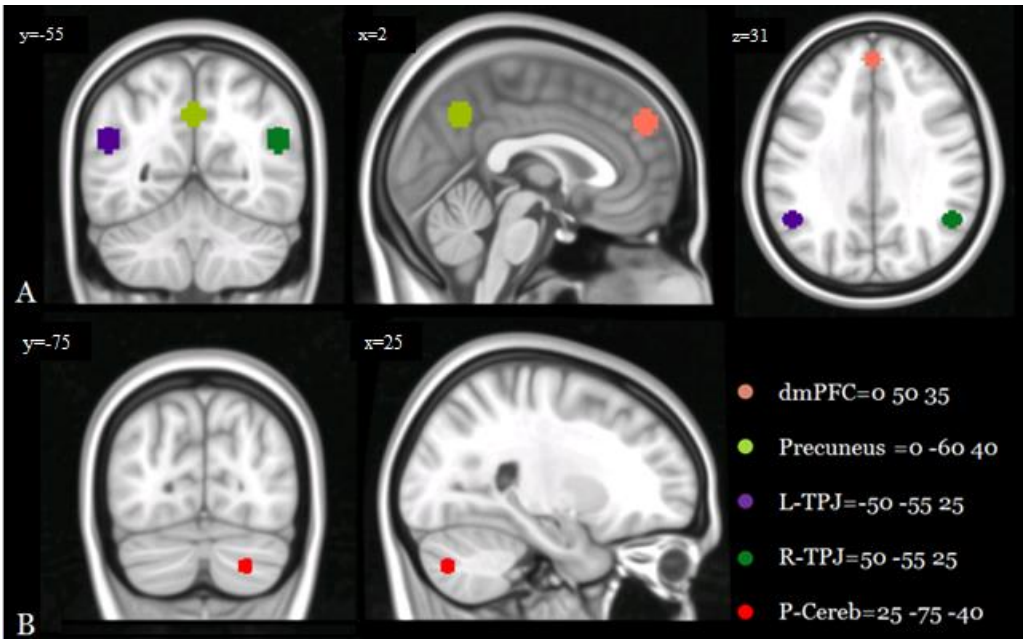


**Figure1. Cerebellar and cerebral regions of interest used to create the graph.**

A) ROIs in the cerebrum (radius sphere:8mm) including dorsal mPFC (with dmPFC as center: 0 50 35) (in pink); precuneus/posterior cingulate (centered at 0 −60 40) (in light green) left and right TPJ (centered at ±50 −55 25)(in violet and dark green, respectively). B) ROI in the cerebellum (radius sphere: 5mm) with right Crus II as center :25 −75 −40 (see Van Overwalle and Marien, 2016) [25]. Regions of interest are shown in y,x,z (A) and y, x (B) slices in the Montreal Neurological Institute space.

In order to obtain a connectivity matrix for each participant, representing the functional network to be tested, each node's mean time course was calculated as the average of the fMRI time series from all voxels within a certain ROI. Correlation matrices were then obtained calculating the correlation between all pairs of nodes' mean signals as described by Serra and colleagues (2016) [39]. In this way, we were able to assess differences in FC between specific cerebellar and cerebral "nodes". A two-sample t-test was used to compare FC matrices between patients and controls, with 5000 permutations and setting the significant p-value at 0.05 (FDR-corrected for multiple comparisons)[29]. Additionally, in order to control for the effect of disease duration across SCA2

patients, the Spearman's correlation test was performed by means SPSS statistic software package to test the association between FC results and the years of illness and clinical disability.

## 3. Results

No subjects were excluded from MRI analysis due to motion artefacts.

NBS analysis showed altered inter-nodal connectivity between specific cerebral and cerebellar mentalizing ROIs (FWE= .05 FDR corrected). Overall, 5 nodes and 5 edges showed differences in SCA2 brains compared to controls. In particular, decreased functional connectivity was found in the following nodes' pairs: dmPFC and right posterior cerebellar Crus II; L-TPJ and R-TPJ; L-TPJ and right posterior cerebellar Crus II; R-TPJ and right posterior cerebellar Crus II; R-TPJ and precuneus (Figure 2). Detailed statistics is reported in Table 2.

As shown by the Spearman's correlation test, FC results were not associated with disease duration and clinical disability in SCA2 patients ($p > 0.05$).

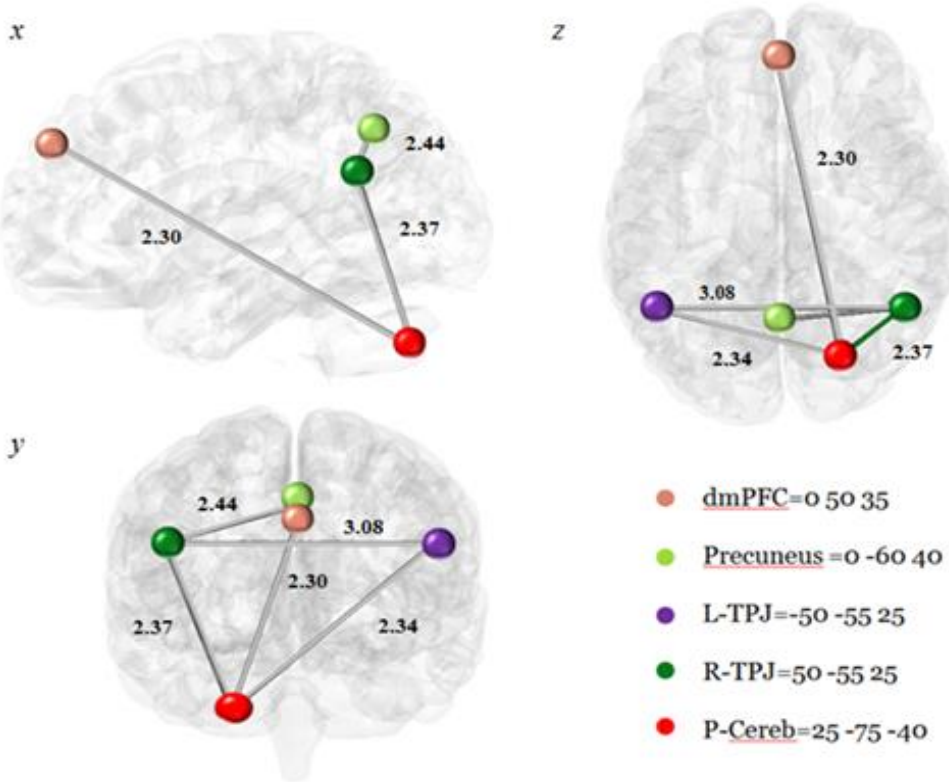

**Figure2. Pairwise regions of significantly decreased functional connectivity in SCA2 patients.** Nodes and edges of significantly decreased functional connectivity in SCA2 patients as assessed by NBS analysis (FWE= .05 FDR corrected). Cerebellar and cerebral nodes in the mentalizing network are shown in different colours in sagittal (x), axial (z) and coronal (y) view. The brain network is visualized using the BrainNet Viewer (https://www.nitrc.org/projects/bnv/) [40].

**Table2.** Pairwise mentalizing nodes of functional underconnectivity.

| **Pairwise Brain regions** | t-values* |
|---|---|
| dmPFC ↔ P-Cereb | **2.30** |
| L-TPJ ↔ R-TPJ | **3.08** |
| R-TPJ ↔ Precuneus | **2.44** |
| L-TPJ ↔ P-Cereb | **2.34** |
| R-TPJ ↔ P-Cereb | **2.37** |

**Table 2.** Difference of functional connectivity into pairwise cerebellar and cerebral regions in patients with SCA2 compared to controls (p-value <0.05 after FDR correction using Network Based statistics).

*t-values are reported; R=right; L=left

## 4. Discussion

Despite the advancing knowledge of cerebellar functions, the specific role that this structure plays in social cognition still remains unclear. In the present study, we used RS-fMRI to interpret functional connectivity alterations and social impairments driven by the cerebellar damage.

In particular, by using a NBS approach [29], FC within cerebello-cerebral mentalizing network was investigated in SCA2 patients according to previous fMRI findings of Van Overwalle and Marien (2016) [25], indicating that the cerebellar posterior Crus II and a set of cerebral cortex regions were specifically involved when social tasks recruit more abstract and complex forms of mentalizing.

Interestingly, altered functional connectivity was found between cerebellar and cerebral mentalizing nodes in patients compared to controls. In particular, decreased functional connectivity was found between dmPFC, bilateral TPJ and right posterior cerebellar Crus II, indicating reduced neural synchronization between these cerebral and cerebellar regions.

Disrupted cerebello-cerebral functional connectivity has been previously demonstrated in people with ASD [19-21], a group consistently reported to show cerebellar structural alterations [41-45]. These observations suggested that a dysfunction of cerebello-cerebral interaction could impact core ASD symptoms, including social and communication deficits and repetitive and stereotyped behaviours. It has been proposed that the sequencing process in the cerebellum is crucial for social functioning since it allows to anticipate action sequences during social interactions and predict and understand others' behaviors [46].

Consistently, cognitive and socio affective impairment has been recently described in the most common SCAs variants in which a degeneration of cerebellum and its connections is typically reported [28]. More recently, further evidence of social impairment has been reported in a group of patients with different cerebellar neurodegenerative pathologies [2], involving both the immediate and automatic perception of mental state and the more complex conceptual level of theory of mind process. Interestingly, authors also focused on the investigation of structural and functional patterns that could subtend social dysfunctions showing decreased FC between cerebellar regions of GM reduction and different cerebral areas involved in specific aspects of social cognition [2]. According to their findings, they proposed that the cerebellar modulatory function on the cortical projection areas may subtend the social cognition process at different levels. This seems to be in line with the recent hypothesis suggesting that the cerebellum has a function-specific role in social mentalizing [24] and that a posterior cerebellar region, corresponding to the Crus II, is selectively involved in more complex and abstract forms of mentalizing together with mentalizing cerebral regions [25]. More specifically, by performing a PPI analysis, authors used a regression model that allows to test how a source area modulates responsiveness of the target area (i.e., cerebellum) given

a cognitive process [27], i.e. social reasoning. In this network, the dmPFC and R-TPJ show forward connectivity to the right Crus II that, in turn, is backward connected to the L-TPJ [25]. According to the evidence that patients with cerebellar neurodegenerative disorders are also impaired in the more complex conceptual level of mentalization [2], one could expect that the cerebellar damage affects the pattern of neural propagation between those cerebellar and cerebral mentalizing regions subtending more abstract social processes. Our results seem to be in line with this hypothesis. In addition to previous findings [2], the NBS analysis in our selected cohort of SCA2 allowed to better clarify functional alteration mechanisms driven by the cerebellar damage indicating that functional disconnection comprised both cortico-cerebellar and cortico-cortical nodes within the network analysed. Overall, these findings provide additional insights indicating that the cerebellar damage specifically associated to SCA2 drives changes between specific nodes of this function-specific network and, thus, impacts complex and abstract forms of social functioning that are independent

from the executive impairment, mostly related to planning, attention and set-shifting abilities, typically reported in SCA2 patients [36; 47-48].

The importance of TPJ, precuneus and the medial part of PFC in social mentalizing has been widely demonstrated (for a review, see Van Overwalle, 2009) [49-57].

Altogether, these regions are known to be part of the Default Mode Network (DMN) [58] an intrinsic functional network indispensable for functions underpinning the social understanding of others [58-59]. From an anatomical point of view, the presence of extensive reciprocal connections between the cerebellum and higher-level cerebral regions has been widely demonstrated [60-62] as well as the functional contribution of the cerebellum, especially Crus I/II, to functional networks that are relevant to cognitive functions and social abilities, also including DMN [16;41]. Generally speaking, cognitive deficits in SCA2 patients have been previously described and related to both structural [36] and functional alterations [63] in the cerebello-cerebral networks.

According to previous studies [37;43;64-65] the present findings have suggested that cognitive impairment may be the result of the disruption of a cerebro-cerebellar circuitry that is influenced by the specific site of cerebellar degeneration. Thus, our hypothesis is that, in the same way as other cognitive domains, the specific pattern of atrophy that can be observed in the course of SCA2 neurodegenerative process may specifically impact, among others, the cerebello-cerebral network that is relevant to higher-level social reasoning. Taken together, the present findings suggest that alterations of complex forms of social mentalizing may represent one of the behavioural correlates in this specific subtype of cerebellar neurodegeneration. Future investigations will aim to better delineate the relation between social profile and FC patterns associated with the SCA2 phenotype. In this regard, an important issue merits to be discussed. Due to the limited number of patients recruited, correlations might go undetected and were not performed in the present study. However, it has to be considered that the strict inclusion criteria and the fact that SCA2 is considered a rare disease, clearly affected the recruitment rate. On the other hand, most standard social cognition tests cannot detect social impairments in cerebellar cohorts because cerebellar patients' symptoms are present in selective domains. In this view, the implementation of specific tasks involving complex and abstract forms of mentalizing [66] will help to detect such a relation in greater patients population. Another issue that merits to be discussed concerns with the possible cortical involvement in symptomatic SCA2 patients. Although this possibility cannot be ruled out, in the present study absence of macroscopic cortical cerebral atrophy was set as patients' inclusion criteria and the total GM volume was not significantly different between SCA2 patients and controls. Furthermore, considering that decreased cerebellar GM volume has been associated with age, one can raises the question about the possible involvement of the cerebellum in healthy ageing [67]. However, since the absence of cerebellar GM atrophy was set as controls' inclusion criteria and SCA2 patients and controls were age-matched, this possibility can be excluded and does not impact the present findings.

In terms of FC results, an important limitation is that the NBS analysis does not allow to make inferences about the direction of connectivity abnormalities. Interestingly, the application of the more advanced DCM to resting-state fMRI data overcomes this limitation since it allows to infer the causal architecture of coupled or distributed dynamical systems by modelling the neuronal dynamics in a network of interacting brain regions or nodes [27]. By applying DCM to task-related fMRI in healthy subjects, it has been shown the presence of bidirectional connections between the cerebellum and the cerebral cortex, thus also confirming that the cerebellum serves as forward controller [26].

Future studies implementing this technique in cerebellar patients will provide important insights into understanding functional impact of the cerebellar damage at level of cerebello-cerebral closed-loop.

## 5. Conclusion

To our knowledge this is the first study investigating the integrity of mentalizing network in SCA2 patients and detecting cerebello-cerebral inter-nodal connectivity changes that can be related to patients' impairment in high-level social processes.

Altogether, the present findings show that the cerebellar dysfunction related to SCA2 neurodegeneration affects a function-specific cerebello-cerebral mentalizing network, thus providing additional insights into understanding functional alteration mechanisms specifically driven by the cerebellar damage associated to SCA2 phenotype.

**Acknowledgements**

This research was partially supported by Italian Ministry of Health (Ricerca Corrente).

**Funding**

This work was supported by the Ministry of Education, Universities and Research (MIUR) to Maria Leggio (Grant Number RM11715C7E67E525) and by the Italian Ministry of Health to Silvia Clausi (Grant Number GR-2013-02354888).

**Conflict of Interest**

The authors declare that they have no conflict of interest

## References


1)Clausi S, Lupo M, Olivito G, Siciliano L, Contento MP, Aloise F, Pizzamiglio L, Molinari M, Leggio M. Depression disorder in patients with cerebellar damage: Awareness of the mood state. J Affect Disord. 2019a; 245:386-393.

2) Clausi S, Olivito G, Lupo M, Siciliano L, Bozzali M, Leggio M. The Cerebellar Predictions for Social Interactions: Theory of Mind Abilities in Patients With Degenerative Cerebellar Atrophy. Front Cell Neurosci 2019b;12:510.

3) Leggio M, Olivito G. Topography of the cerebellum in relation to social brain regions and emotions. Handb Clin Neurol 2018; 154:71-84. Review.

4)Lupo M, Olivito G, Iacobacci C, Clausi S, Romano S, Masciullo M, Molinari M, Cercignani M, Bozzali M, Leggio M. The cerebellar topography of attention sub-components in spinocerebellar ataxia type 2. Cortex 2018a;108:35-49.

5)Lupo M, Olivito G, Siciliano L, Masciullo M, Molinari M, Cercignani M, Bozzali M, Leggio M. Evidence of cerebellar involvement in the onset of a manic state. Front Neurol 2018b; 9:774.

6)Lupo M, Olivito G, Siciliano L, Masciullo M, Bozzali M, Molinari M, Leggio M. Development of a Psychiatric Disorder Linked to Cerebellar Lesions. Cerebellum 2018c;17(4):438-446.

7)Clausi S, Iacobacci C, Lupo M, Olivito G, Molinari M, Leggio M. The role of the cerebellum in unconscious and conscious processing of emotions: A review. Applied Sciences (Switzerland) 2017;7(5): 521. Review.

8)Hoche F, Guell X, Vangel MG, Sherman JC, Schmahmann JD. The cerebellar cognitive affective/Schmahmann syndrome scale. Brain 2018; 141:248–270.

9)Tedesco AM, Chiricozzi FR, Clausi S, Lupo M, Molinari M, Leggio MG. The cerebellar cognitive profile. Brain 2011; 134:3672–3686.

10) Stoodley CJ, and Schmahmann JD. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex 2010; 46:831–844.

11)Mar RA. The neural bases of social cognition and story comprehension. Annu Rev Psychol 2011; 62: 103–134.

12) Calder AJ, Lawrence AD, Young AW. Neuropsychology of fear and loathing. Nat Rev Neurosci 2001; 2: 352–363.

13)Kipps CM, Duggins AJ, McCusker EA, Calder AJ. Disgust and happiness recognition correlate with anteroventral insula and amygdala volume respectively in preclinical Huntington's disease. J Cogn Neurosci 2007; 19: 1206–1217.

14) Biswal BB, Van Kylen J, Hyde JS. Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. NMR Biomed 1997;10:165–70.

15)Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V, Greicius MD. Distinct cerebellar contributions to intrinsic connectivity networks. J Neurosci 2009; 29:8586–8594.

16)Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BT. The organization of the human cerebellum estimated by intrinsic functional connectivity. J Neurophysiol 2011; 106,2322-45.

17)Krienen FM, Buckner RL. Segregated frontocerebellar circuits revealed by intrinsic functional connectivity. Cereb Cortex 2009; 19: 2485–2497.

18) Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 2011; 106: 1125–1165.

19)Olivito G, Lupo M, Laghi F, Clausi S, Baiocco R, Cercignani M, Bozzali M, Leggio M. Lobular patterns of cerebellar resting-state connectivity in adults with Autism Spectrum Disorder. Eur J Neurosci. 2018a;47(6):729-735.

20)Olivito G, Clausi S, Laghi F, Tedesco AM, Baiocco R, Mastropasqua C, Molinari M, Cercignani M, Bozzali M, Leggio M. Resting-state functional connectivity changes between dentate nucleus and cortical social brain regions in autism spectrum disorders. Cerebellum 2017a; 16: 283–292.

21)Khan AJ, Nair A, Keown CL, Dakto MC, Lincoln AJ, Muller RA. Cerebro-cerebellar Resting state Functional Connectivity in Children and adolescents with Autism Spectrum Disorder. Biol Psychiatry 2015;78:625–34.

22)D'Mello AM and Stoodley CJ. Cerebro-cerebellar circuits in autism spectrum disorder. Front Neurosci. 2015; 9:408. Review

23)Van Overwalle F, Baetens K, Mariën P, Vandekerckhove M. Social cognition and the cerebellum: a meta-analysis of over 350 fMRI studies. Neuroimage 2014; 86: 554–572.

24)Van Overwalle F, D'aes T, Marie¨n P. Social cognition and the cerebellum: a meta-analytic connectivity analysis. Hum Brain Map 2015; 36: 5137–5154.

25)Van Overwalle F, Marie¨n P. Functional connectivity between the cerebrum and cerebellum in social cognition: a multi-study analysis. Neuroimage 2016; 124: 248–255.

26)Van Overwalle F, Van de Steen F, Mariën P. Dynamic causal modeling of the effective connectivity between the cerebrum and cerebellum in social mentalizing across five studies. Cogn Affect Behav Neurosci 2019a;19(1):211-223.

27)Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Functional connectivity: the principal-component analysis of large (PET) data sets. J Cereb Blood Flow Metab 1993; 13:5–14.

28) Giacondo F, Curcio G. Spinocerebellar ataxia: a critical review of cognitive and socio-cognitive deficits. Int J Neurosci. 2018;128(2):182-191.

29)Zalensky A, Fornito A, Bullmore ET. Network-based statistic, identifying differences in brain networks. Neuroimage 2010; 53:1197–1207.

30)Della Nave R, Ginestroni A, Tessa C, Cosottini M, Giannelli M, Salvatore E, Sartucci F, De Michele G, Dotti MT, Piacentini S, Mascalchi M. Brain structural damage in spinocerebellar ataxia type 2. A voxel-based morphometry study. Mov Disord 2008; 23(6):899–903.

31)Estrada R, Galarraga J, Orozco G, Nodarse A, Auburger G. Spinocerebellar ataxia 2 (SCA2),: morphometric analyses in 11 autopsies. Acta Neuropathol (Berl) 1999; 97:306–310.

32)Iwabuchi K, Tsuchiya K, Uchihara T, Yagishita S. Autosomal dominant spinocerebellar degenerations. Clinical, pathological, and genetic correlations. Rev Neurol (Paris) 1999; 155:255–270.

33)Trouillas P, Takayanagi T, Hallett M, Currier RD, Subramony SH, Wessel K, Bryer A, Diener HC, Massaquoi S, Gomez CM, Coutinho P, Ben Hamida M, Campanella G, Filla A, Schut L, Timann D, Honnorat J, Nighoghossian N, Manyam B. International cooperative ataxia rating scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. J Neurol Sci 1997; 145:205–211.

34)Wechsler D. Wais-R. Wechsler Adult Intelligence Scale Revised. Firenze: Organizzazioni Speciali, 1981.

35)Orsini A, Laicardi C. WAIS-R-Contributo alla Taratura Italiana, Firenze Organizzazioni Speciali, 1997.

36) Olivito G, Lupo M, Iacobacci C, Clausi S, Romano S, Masciullo M, Molinari M, Cercignani M, Bozzali M, Leggio M. Structural cerebellar correlates of cognitive functions in spinocerebellar ataxia type 2. J Neurol 2018b; 265(3):597-606.

37)Olivito G, Lupo M, Iacobacci C, Clausi S, Romano S, Masciullo M, Molinari M, Cercignani M, Bozzali M, Leggio M. Microstructural MRI basis of the cognitive functions in patients with Spinocerebellar ataxia type 2. Neuroscience 2017b; 366:44–53.

38)Brett M, Anton JL, Valabregue R, Poline JB. Region of interest analysis using an SPM toolbox [abstract] Presented at the 8th International Conference on Functional Mapping of the Human Brain, June 2-6, 2002, Sendai, Japan. Available on CD-ROM in NeuroImage Vol 16, No 2.

39)Serra L, Cercignani M, Bruschini M, Cipolotti L, Mancini M, Silvestri G, Petrucci A, Bucci E, Antonini G, Licchelli L, Spanò B, Giacanelli M, Caltagirone C, Meola G, Bozzali M. "I know that you know that I know", neural substrates associated with social cognition deficits in DM1 patients. PLoS One 2016;11(6).

40)Xia M, Wang J, He Y. BrainNet Viewer, a network visualization tool for human brain connectomics. PLoS One 2013;8.

41)D'Mello AM, Crocetti D, Mostofsky SH, Stoodley CJ. Cerebellar grey matter and lobular volumes correlate with core autism symptoms. Neuroimage Clin 2015; 7: 631–639.

42)Allen G. The cerebellum in Autism. Clinical Neuropsychiatry 2005; 2(6):321-337.

43)Fatemi SH, Halt AR, stary JM, Kanodia R, Schulz SC, Realmuto GR. Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebella cortices. Biological Psychiatry 2002; 52, 8, 805-810.

44)Carper RA and Courchesne E. Inverse correlation between frontal lobe and cerebellum sizes in children with autism. Brain 2000; 123:836-844.

45)Courchesne E, Townsend J, Saitoh O. The brain in infantile autism: Posterior fossa structures are abnormal. Neurology 1994; 44:214-223.

46) Van Overwalle F, Manto M, Leggio M, Delgado-García JM. The sequencing process generated by the cerebellum crucially contributes to social interactions. Med Hypothesis 2019;128:33-42.

47)Klinke I, Minnerop M, Schmitz-Hübsch T, Hendriks M, Klockgether T, Wüllner U, Helmstaedter C. Neuropsychological features of patients with Spinocerebellar ataxia (SCA), types 1,2,3, and 6. Cerebellum 2010; 9:433–442.

48)Fancellu R, Paridi D, Tomasello C, Panzeri M, Castaldo A, Genitrini S, Soliveri P, Girotti F Longitudinal study of cognitive and psychiatric functions in spinocerebellar ataxia types 1 and 2. J Neurol 2013; 260:3134–3143.

49)Van Overwalle F. Social cognition and the brain: a meta-analysis. Hum BrainMapp 2009; 30: 829–858.

50)Schurz M, Radua J, Aichhorn M, Richlan F, Perner J. Fractionating theory of mind: a meta-analysis of functional brain imaging studies. Neurosci Biobehav Rev. 2014; 42:9-34.

51)Saxe R and Powell LJ. It's the thought that counts: Specific brain regions for one component of theory of mind. Psychological Science 2006; 17: 692–699.

52)Saxe R and Wexler A. Making sense of another mind: The role of the right temporo-parietal junction. Neuropsychologia 2005; 43:1391–1399.

53)Ma N, Vandekerckhove M, Van Hoeck N, Van Overwalle F. Distinct recruitment of temporo-parietal junction and medial prefrontal cortex in behavior understanding and trait identification. Soc Neurosci 2012;7(6):591-605.

54)Harris LT, Todorov A, Fiske ST. Attributions on the brain: Neuro-imaging dispositional inferences, beyond theory of mind. NeuroImage 2005; 28: 763–769.

55)Saxe R. Uniquely human social cognition. Current Opinion in Neurobiology 2006; 16: 235–239.

56)Decety J and Sommerville JA. Shared representations between self and other: a social cognitive neuroscience view. Trends Cogn Sci 2003;7(12):527-33.

57)Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. Brain J Neurol 2006; 129(Pt 3): 564-583.

58)Raichle EM, MacLeod AM, Snyder AZ, PowersWJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A 2001;98:676–82.

59)Schilbach L, Eickhoff SB, Rotarska-Jagiela A, Fink GR, Vogeley K. Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the default system of the brain. Conscious Cogn 2008;17:457–67.

60)Schmahmann JD. An emerging concept: the cerebellar contribution to higher function. Arch Neurol 1991; 48:1178–1187.

61)Middleton FA and Strick PL Cerebellar projections to the prefrontal cortex of the primate. J Neurosci 2001; 21:700–712.

62)Kelly RM and Strick PL. Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J Neurosci 2003; 23: 8432–8444.

63)Olivito G, Cercignani M, Lupo M, Iacobacci C, Clausi S, Romano S, Masciullo M, Molinari M, Bozzali M, Leggio M. Neural substrates of motor and cognitive dysfunctions in SCA2 patients: A network based statistics analysis. Neuroimage Clin 2017c;14:719-725.

64)Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. NeuroImage 2009; 44:489–501.

65)Kawai Y, Suenaga M, Watanabe H, Sobue G. Cognitive impairment in spinocerebellar degeneration. Eur Neurol 2009; 61:257–268.

66)Van Overwalle F, De Coninck S, Heleven E, Perrotta G, Taib NOB, Manto M, Mariën P. The role of the cerebellum in reconstructing social action sequences: a pilot study. Soc Cogn Affect Neurosci. 2019b;14(5):549-558.

67) Filip P, Gallea C, Lehéricy S, Lungu O, Bareš M. Neural Scaffolding as the Foundation for Stable Performance of Aging Cerebellum. Cerebellum 2019;18(3):500-510.

Figure1

Click here to access/download;Figure;Figure1.tif

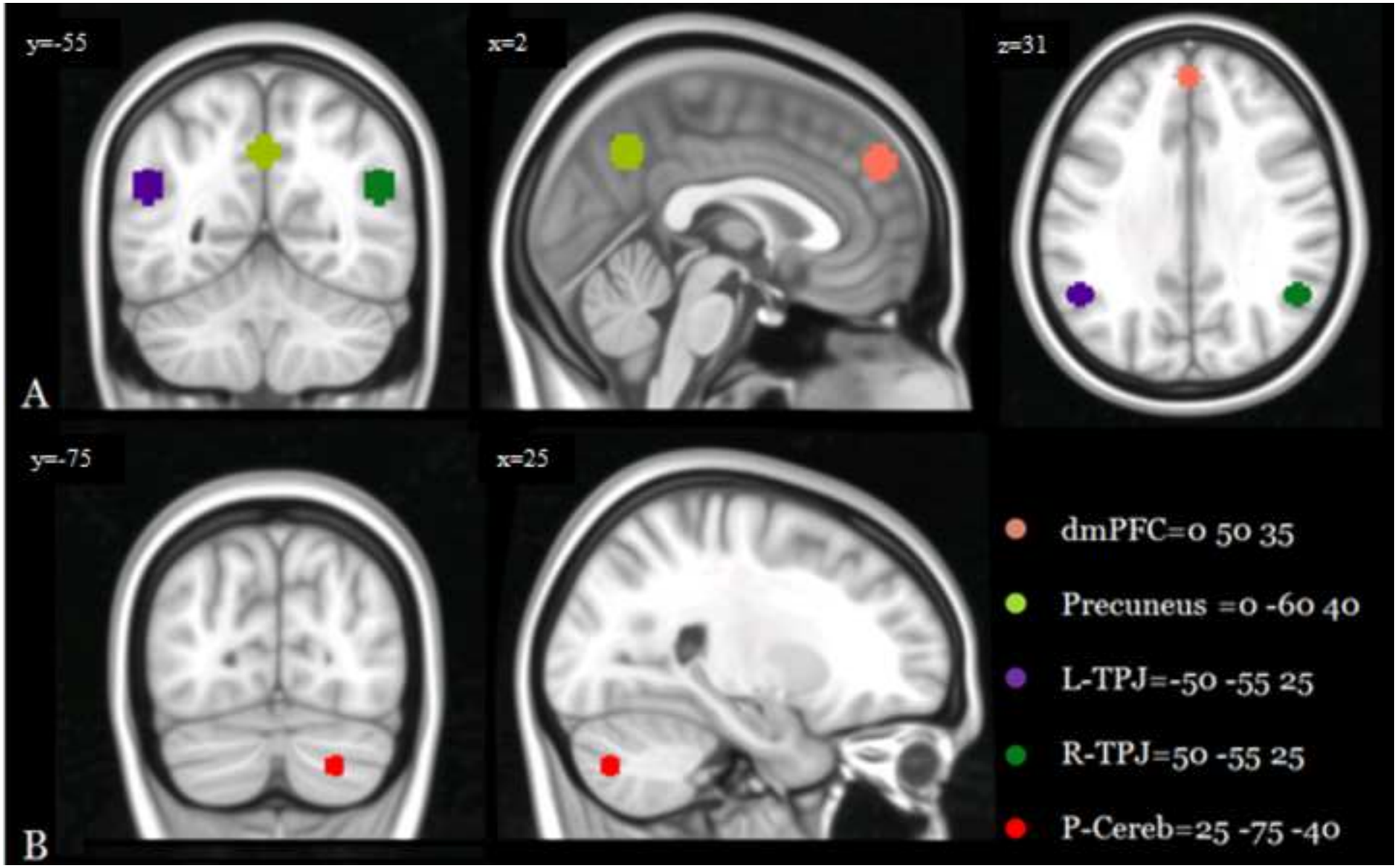

Figure2

Click here to access/download;Figure;Figure2.tif

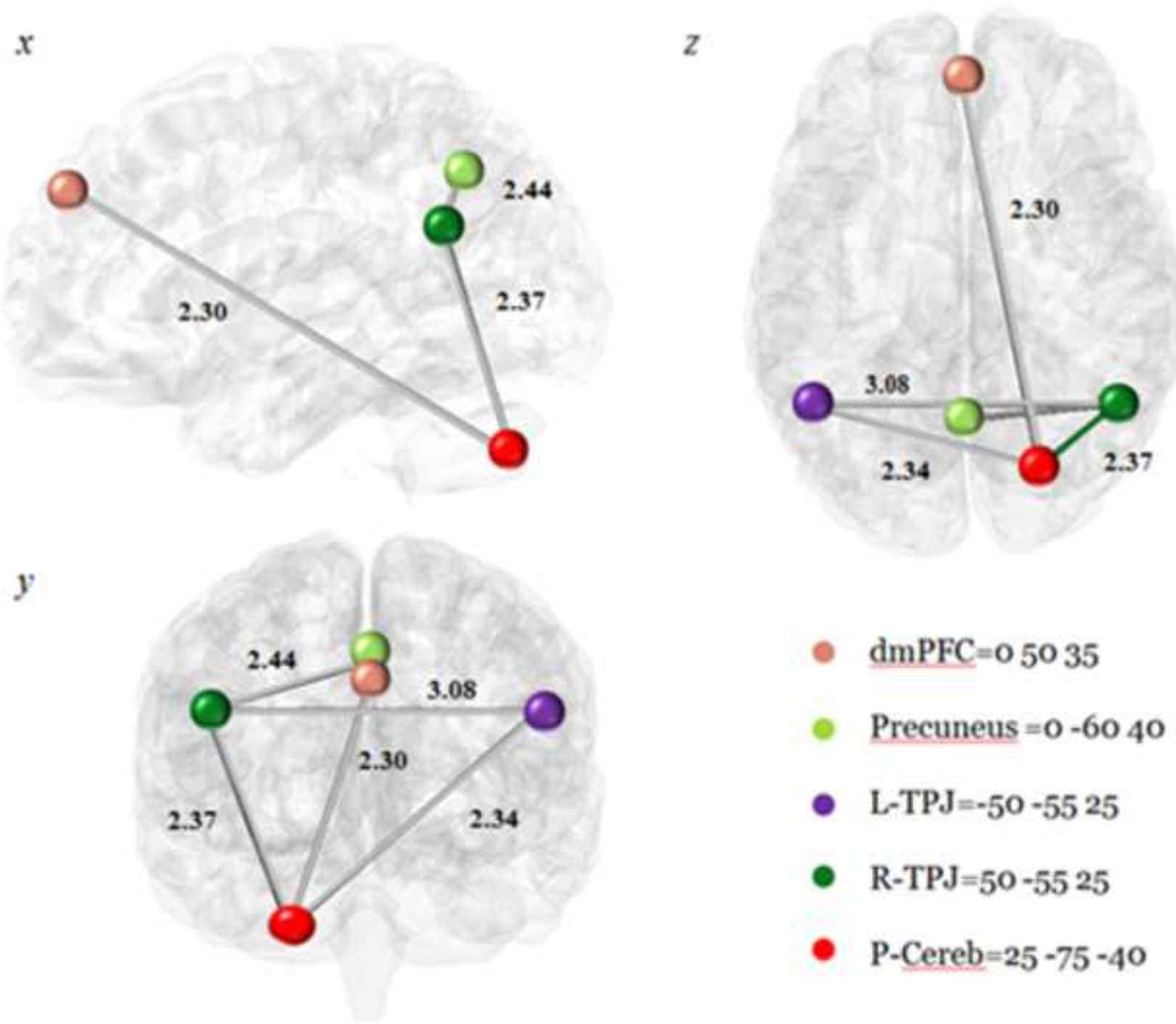

**Table 1.** Demographic characteristics and motor deficit scores of the patients.

| Case code | Age | Gender | IQ | Disease duration (years) | ICARS TOTAL SCORES | CGA Repeats |
|---|---|---|---|---|---|---|
| CA-1 | 42 | F | 74 | 1 | 47 | 22/39 |
| CA-2 | 42 | F | 81 | 1 | 28 | 14/47 |
| CA-3 | 54 | F | 85 | 1 | 27 | 22/37 |
| CA-4 | 36 | F | 91 | 8 | 37 | 22/42 |
| CA-5 | 65 | M | 82 | 3 | 27 | 22/35 |
| CA-6 | 44 | F | 98 | 13 | 28 | * |
| CA-7 | 62 | F | 75 | 4 | 31 | 22/37 |
| CA-8 | 41 | M | 91 | 3 | 18 | 22/38 |
| CA-9 | 42 | M | 81 | 1 | 24 | 22/39 |
| CA-10 | 44 | M | 110 | 7 | 17 | 22/39 |

**Table 1.** The table reports for each patient age, gender, disease duration (in years) , intellectual level as assessed by the Wechsler Adult Intelligence Scale-Revised (IQ: Intelligence Quotient), total motor scores as assessed by the International Cooperative Ataxia and CAG repeats. *Genetic data are not available for the patient CA-6 because, at the time of the diagnosis, the genetic testing did not include the triplets number counting.

**Table2.** Pairwise mentalizing nodes of functional underconnectivity.

| **Pairwise Brain regions** | t-values* |
|---|---|
| dmPFC ↔ P-Cereb | **2.30** |
| L-TPJ ↔ R-TPJ | **3.08** |
| R-TPJ ↔ Precuneus | **2.44** |
| L-TPJ ↔ P-Cereb | **2.34** |
| R-TPJ ↔ P-Cereb | **2.37** |

**Table 2.** Difference of functional connectivity into pairwise cerebellar and cerebral regions in patients with SCA2 compared to controls (p-value <0.05 after FDR correction using Network Based statistics).

*t-values are reported; R=right; L=left